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Factors associated with chronic kidney disease progression in Australian nephrology practices

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Abstract

Background/Aims: Chronic kidney disease (CKD) is a major health issue worldwide. The aim of this study was to explore factors associated with CKD progression in Australian nephrology practices. Methods: This was a retrospective study utilising an electronic medical record (EMR), Audit4 (Software for Specialists, Australia). The baseline visit was defined as the first entry into the EMR. The primary outcome was the rate of change in estimated glomerular filtration rate (eGFR). Results: 1,328 patients were included with a mean eGFR at baseline of 37.4 ± 0.7 ml/min/1.73 m2, a mean follow-up of 17.7 months and a mean annual rate of change in eGFR of −0.84 ± 0.26 ml/min/1.73 m2. Univariate analysis demonstrated that women, smokers, and patients prescribed erythropoiesis-stimulating agents (ESA) had a significantly more rapid decline in eGFR (p = 0.007, 0.033, and 0.003, respectively). On multivariate analysis: gender, age, prescription of ESA and phosphate binders, and baseline eGFR were significantly associated with CKD progression (p = 0.003, 0.004,

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Factors Associated with Chronic Kidney Disease Progression in Australian Nephrology Practices

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Key Words

Chronic kidney failure · Disease progression · Electronic health records · Natural history

Abstract

Background/Aims: Chronic kidney disease (CKD) is a major health issue worldwide. The aim of this study was to explore factors associated with CKD progression in Australian nephrology practices. ***Methods:*** This was a retrospective study utilising an electronic medical record (EMR), Audit4 (Software for Specialists, Australia). The baseline visit was defined as the first entry into the EMR. The primary outcome was the rate of change in estimated glomerular filtration rate (eGFR). ***Results:*** 1,328 patients were included with a mean eGFR at baseline of 37.4 ± 0.7 ml/min/1.73 m^2, a mean follow-up of 17.7 months and a mean annual rate of change in eGFR of −0.84 ± 0.26 ml/min/1.73 m^2. Univariate analysis demonstrated that women, smokers, and patients prescribed erythropoiesis-stimulating agents (ESA) had a significantly more rapid decline in eGFR ($p = 0.007$, 0.033, and 0.003, respectively). On multivariate analysis: gender, age, prescription of ESA and phosphate binders, and baseline eGFR were significantly associated with CKD progression ($p = 0.003$, 0.004, <0.001, 0.029, and <0.001, respectively). ***Conclusions:*** This study identifies potential factors associated with CKD progression in a population referred to nephrologists, but current data quality may result in bias. Implementation of changes in the format of data collection is required so that busy clinicians record essential information to enable this to become a more accurate and reliable research tool.

Introduction

Chronic kidney disease (CKD) is a common problem in Australia affecting approximately 11.2% of the adult population [1]. In addition, it is a growing health concern with the number of dialysis patients in Australia increas-

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ing every year [2]. As a consequence of the high cost of dialysis and the increasing numbers, the expenditure for end-stage kidney disease (ESKD) management between 2005 and 2010 was estimated at USD 5 billion [3]. Furthermore, recent projections in Australia suggest this will more than double to over USD 11.3 billion by 2020 [4]. Similar trends are seen worldwide [5].

Most of our knowledge on the progression of CKD is derived from interventional clinical trials or observational cohort studies performed in populations that incidentally had CKD [6–10]. Outcomes from these studies suggest that the management of individual CKD patients include tight control of diabetes and blood pressure and the prescription of specific medications (e.g. statins, renin-angiotensin system antagonists) [11]. However, evidence that these and other interventions slow CKD progression has been at times contradictory and the effect of multiple interventions on an individual is unclear [11–15].

We examined a population of CKD patients under the clinical supervision of nephrologists because of a higher likelihood of accurate identification and simultaneous management according to available guidelines and best practice, of multiple factors [14, 16–18]. Despite this expert care, patients still progress to ESKD. We selected nephrology practices using electronic medical records (EMR) in patient management to capture longitudinal data on large cohorts of patients in a cost-efficient manner. The aim of this study was to explore the factors that are associated with progression of CKD in a referred population spread throughout Australia.

Methods

This was a retrospective study utilising Audit4 (Software 4 Specialists, Australia), which is an EMR utilised by over 40 nephrology practices in Australia. The electronic Kidney Disease National Audit Alliance (eKiDNAA) was established in September 2010 and incorporated all Australian Audit4 nephrology users. The aim of this collaboration was to facilitate research in CKD. Laboratory data was uploaded electronically by local pathology services to the Audit4 database locally. Conditions and medications were entered from drop-down lists by the treating nephrologist. No formal auditing of data quality was performed as part of this study.

Referred prevalent and incident adult patients were included in this study if they had a minimum of two serum creatinine measurements at least 90 days apart. The baseline visit was defined as the time of the first entry of the patient into Audit4. Follow-up was defined as the period until the most recent serum creatinine measurement at the time of data extraction. All patient data were de-identified and compiled into a central database for analysis. Those patients in ESKD at baseline (i.e. dialysis or kidney transplant) were excluded from the study. Ethics approval for this study was obtained from the University of New South Wales Ethics Committee.

Serum creatinine was measured using an assay that was isotope dilution mass spectrometry (IDMS) calibrated which was traceable to National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 909b-2. NIST SRM 909b-2 is a lyophilized material traceable to the IDMS method, and hence traceable to a calibration panel prepared by the Cleveland Clinic Research Laboratory. Estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine measurement using the 4 variable Modification of Diet in Renal Disease (MDRD) equation, eGFR (ml/min/1.73 m^2) = 175 × [creatinine (μmol/l) × 0.0113]$^{-1.154}$ × age (years)$^{-0.203}$ (×0.742 if female) [19].

The primary outcome was the rate of change in eGFR (ml/min/1.73 m^2 per year) over the study period. The Audit4 database was interrogated and the independent variables examined included cause of CKD, gender, age, race, medications (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, statins and phosphate binders) and co-morbidities (e.g. history of vascular disease, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease and smoking). Additional biochemical and haematological data were collected, including serum bicarbonate, calcium, phosphate, parathyroid hormone, and haemoglobin concentration.

Statistical Methods

The rate of change in eGFR was compared between the individual causes of CKD using t test. Simple linear regression analysis was performed with the change in eGFR per year as the dependent variable. Variables that had a $p < 0.20$ were included into a multiple linear regression analysis, along with those considered theoretically important (i.e. age and phosphate binder use) [1]. The a priori statistical analysis plan included cause of CKD, vascular co-morbidities, blood pressure and a composite of spot urine albumin to creatinine ratio (ACR) and protein to creatinine ratio (PCR), for those without ACR data. Subjects were censored for death or ESKD. A p value <0.05 was deemed statistically significant.

Results

1,328 participants were included from nephrology practices in four States of Australia (New South Wales, Queensland, Victoria, and Western Australia). Mean eGFR at baseline was 37.4 ± 0.7 ml/min/1.73 m^2 with a mean follow-up of 17.7 months (range 7–26 months) (table 1). The mean annual rate of change in eGFR was −0.84 ± 0.26 ml/min/1.73 m^2. There was no significant difference in the rate of change in eGFR between individual causes of CKD on univariate analysis: glomerulonephritis −0.59 ± 12.2 ml/min/1.73 m^2/year; diabetic nephropathy −1.48 ± 8.49 ml/min/1.73 m^2/year; hypertension/renovascular disease −0.82 ± 5.41 ml/min/1.73 m^2/year,

Table 1. Baseline demographics and data

Serum creatinine, μmol/l	189.1 ± 4.9
eGFR, ml/min/1.73 m^2	37.4 ± 0.7
Age, years	69.2 ± 0.4
Male gender	56.8% (756)
History of vascular disease	32.5% (432)
History of cardiovascular disease	22.7% (302)
History of cerebrovascular disease	7.7% (102)
History of peripheral vascular disease	13.5% (180)
History of smoking	10.8% (143)
Cause of CKD	
Glomerulonephritis	24.5% (326)
Diabetic nephropathy	28.4% (378)
Hypertension/renovascular disease	11.1% (148)
Polycystic kidney disease	2.9% (39)
Others	33.1% (439)
RAAS inhibitor use	61.7% (820)
ESA use	19.8% (252)
Phosphate binder use	18.6% (248)
Statin use	48.4% (644)
Systolic blood pressure, mm Hg	137 ± 0.8
Diastolic blood pressure, mm Hg	76 ± 0.4
Serum phosphate, mmol/l	1.28 ± 0.01
Serum calcium, mmol/l	2.34 ± 0.005
Serum bicarbonate, mmol/l	25.6 ± 0.1
Median C-reactive protein, mg/l	38.9
Haemoglobin, g/l	123.0 ± 0.6
Glycated haemoglobin, %	7.0 ± 0.08
Spot urine albumin:creatinine, mg/mmol	57.8 ± 6.4
Spot urine protein:creatinine, mg/mmol	102.6 ± 8.5

Values are mean ± SEM or percentages with numbers in parentheses.

Table 2. Univariate analysis of the association between independent variables and change in eGFR

Variable	β coefficient	p value
Male gender	1.40	0.007
Age	−0.12	0.43
History of vascular disease	−0.93	0.088
History of cardiovascular disease	−0.77	0.21
History of cerebrovascular disease	−0.23	0.81
History of peripheral vascular disease	−0.77	0.30
History of smoking	−1.76	0.033
RAAS inhibitor use	−0.33	0.53
ESA use	−1.96	0.003
Phosphate binder use	−0.62	0.35
Statin use	−0.26	0.99
Systolic blood pressure >130 mm Hg	0.14	0.87
Diastolic blood pressure >80 mm Hg	−1.06	0.18
Serum phosphate >1.25 mmol/l	1.04	0.08
Serum calcium	−0.68	0.43
Serum bicarbonate	−0.26	0.80
Haemoglobin >110 g/l	−1.38	0.045
Bilirubin >17	−0.53	0.65
Glycated haemoglobin	−1.45	0.004
7.0–7.9%		
>8.0%		
Spot urine albumin:creatinine	−0.004	0.37
Spot urine protein:creatinine	−0.001	0.85

and autosomal dominant polycystic kidney disease (ADPKD) −3.97 ± 15.06 ml/min/1.73 m^2/year (p = 0.246).

Univariate analysis demonstrated that female gender, history of smoking, erythropoiesis-stimulating agent (ESA) use, high haemoglobin (>110 g/l) and glycated haemoglobin were statistically significantly associated with a greater rate of eGFR decline (table 2).

Multivariate regression analysis showed the factors significantly associated with rate of eGFR decline included gender, age, ESA and phosphate binder use, and baseline eGFR in model 1 (table 3). Inclusion of additional variables reduced the number of participants that could be included in further modelling. Including proteinuria in the modelling (model 2) maintained age, ESA use and baseline eGFR as significant variables associated with the progression of CKD, but the significant association with gender, and phosphate binder use was no longer apparent. Subsequent inclusion of blood pressure, serum phosphate and baseline haemoglobin (model 3) maintained age, ESA use, and baseline eGFR as being significantly associated with CKD progression, in addition haemoglobin >110 g/l and diastolic blood pressure >80 mm Hg were also independently significant. Neither serum phosphate nor proteinuria were statistically significantly associated with progression of CKD in these models.

Discussion

Utilising an EMR database to perform a retrospective study on a cohort of referred CKD patients under the clinical supervision of nephrologists, we identified that female gender, ESA use, phosphate binder use, age and baseline eGFR were significantly associated with more rapid decline in kidney function.

CKD is a risk factor for cardiovascular outcomes and mortality [20]. In addition, the rate of decline in kidney function is associated with poor outcomes [21]. Some of the factors that have been demonstrated (to varying levels

Table 3. Multivariate analysis of the association between independent variables and annual rate of change of eGFR

Variable	Model 1 (n = 1,328, r^2 = 0.10)		Model 2 (n = 1,328, r^2 = 0.09)		Model 3 (n = 216, r^2 = 0.20)	
	β coefficient	p value	β coefficient	p value	β coefficient	p value
Male gender	1.54	0.003	1.36	0.087	0.10	0.94
Age	−0.06	0.004	−0.07	0.017	−0.11	0.015
History of vascular disease	−0.69	0.52	−0.47	0.80	4.43	0.14
History of cardiovascular disease	0.04	0.97	−0.51	0.77	−3.12	0.27
History of peripheral vascular disease	0.06	0.95	0.53	0.74	−1.79	0.45
History of smoking	−1.24	0.12	−0.75	0.54	−0.39	0.84
Glomerulonephritis	1.00	0.14	0.88	0.41	3.01	0.09
Diabetic nephropathy	−0.75	0.18	−1.13	0.20	−2.84	0.06
Hypertension/renovascular disease	−0.35	0.67	−0.31	0.79	0.06	0.98
ADPKD	−2.54	0.090	−3.35	0.16	−6.27	0.25
Obstructive uropathy	0.28	0.84	−0.04	0.98	−1.84	0.60
ESA use	−3.26	<0.001	−3.14	0.004	−5.51	0.001
Phosphate binder use	−1.46	0.029	−1.67	0.134	−0.69	0.72
Baseline eGFR	−0.13	<0.001	−0.14	<0.001	−0.21	<0.001
ACR/PCR composite			−0.01	0.80	−0.01	0.20
Diastolic blood pressure >80 mm Hg					−3.24	0.018
Serum phosphate >1.25 mmol/l					0.33	0.82
Haemoglobin >110 g/l					−5.40	0.002

of evidence) to be associated with progression of CKD include elevated blood pressure, proteinuria, poor diabetic control, RAAS inhibitors, and serum bicarbonate [6–8, 11, 13, 22, 23]. In a cohort of patients cared for by nephrologists it would be hoped that most of the major risk factors would be managed in line with best practice, in particular blood pressure control, minimisation of proteinuria and control of diabetes [14]. The relatively slow progression in eGFR of −0.84 ± 0.26 ml/min/1.73 m^2/year seen in our cohort therefore is not surprising and comparable to other studies [14, 24, 25].

The presumed maximal management of known risk factors (reflected in the low proteinuria and high RAAS use) in this referred cohort may explain our inability to identify a significant association between these risk factors and progression of CKD. Alternatively, it may reflect a lack of power due to missing data, as was seen in a Taiwanese study on referred patients [24].

In a large USA cohort study, age and baseline kidney function were identified as being associated with an increased risk of development of ESKD, but female gender was not [26]. Age is a central component of the formula used to calculate eGFR from serum creatinine and therefore can be expected to be associated with eGFR [23]. The association of female gender with CKD progression was unexpected as there is a preponderance of men on dialysis [27].

The associations seen in this analysis do not imply causation. Exploration of the definition of some of these variables suggests the reverse. For example, ESA use was documented as being present if it was prescribed at any stage during the follow-up period and so it is likely that those patients that progressed faster were more likely to develop anaemia and be prescribed an ESA. In addition, our identified association with a haemoglobin >110 g/l may reflect this same population of patients prescribed an ESA, as target haemoglobin in these patients, until recently, was >110 g/l. The design of our study is unable to discriminate between factors that are causative and those that are associative.

The randomised controlled trial is the gold standard for attributing causation. It is a valid design for questions of the efficacy of a single treatment intervention, but is an imperfect fit for evaluating multiple simultaneous interventions whose interactions may not be known. Studies of human disease do not always lend themselves to randomisation or other conditions of the randomised controlled trial. In these instances, non-randomised trials that are well conducted may still produce clinically valid and reliable data in these complex environments.

EMRs have become increasingly commonplace amongst healthcare providers and have created the opportunity to not only improve individual patient care but also to potentially supply more global information about disease processes [28, 29]. The uptake of the same EMR by multiple nephrologists throughout Australia has created an opportunity to examine their utility in testing hypotheses in reasonable sized populations.

Our study however has a number of limitations. Our results were confounded by the limitations of the EMRs as a research tool [28, 29]. Incomplete data collection compromised the quality of the analyses. We found the addition of variables into multivariate models reduced the number of patients available for inclusion, which is one of the main strengths of using the EMR. Glycated haemoglobin for example was not included in any of the models due to an insufficient dataset of less than 100 participants. This study is also limited by its retrospective and observational design. The results can therefore only show associations and require confirmation in long-term prospective observational studies. The study is also subject to recruitment bias with participating nephrologists possibly being more proactive in the management of CKD and not representative of all CKD care in Australia.

In conclusion we have identified a number of factors that are associated with progression of CKD in patients managed by nephrologists in Australia. Our results demonstrate the utility of using aggregated data collected electronically. They also demonstrate that inadequate data quality limits the power of aggregated data. We are exploring different data capture tools with the aim of improving data integrity while still maintaining the record as a useful part of everyday practice. The potential to collect data on large numbers of patients longitudinally in a cost-effective way is extremely appealing.

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Disclosure Statement

David Hoffman is an owner of Software for Specialists that developed *Audit4*. There are no other conflicts of interest to disclose.

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